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| 10/713,978 | 11/14/2003 | Michael B. Yaffe | 01997/545003 | 5853 |
| 21559 | 7590 | 03/31/2008 | | |
| CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110 | | | EXAMINER STEADMAN, DAVID J | |
| | | | ART UNIT 1656 | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

| | | | |
|------------------------------|--------------------------------------|-------------------------------------|--|
| Office Action Summary | Application No. 10/713,978 | Applicant(s) YAFFE ET AL. | |
| | Examiner David J. Steadman | Art Unit 1656 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 February 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13, 17-25, 27-36 and 39-44 is/are pending in the application.
- 4a) Of the above claim(s) 2-13, 17-25 and 27-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 39-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/8/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/8/08 has been entered.

[2] Claims 1-13, 17-25, 27-36, and 39-44 are pending in the application.

[3] Receipt of an information disclosure statement, filed on 2/8/08, is acknowledged.

[4] Applicant's arguments filed on 2/8/08 in response to the Office actions mailed on 8/6/07 and 12/28/07 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[6] Claims 2-13, 17-25, and 27-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 10/20/06.

[7] Claims 1 and 39-44 are being examined on the merits.

Claim Rejections - 35 USC § 112, Second Paragraph

[8] The rejection of claims 1 and 39-44 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's instant amendment to the claims.

Claim Rejections - 35 USC § 112, First Paragraph

[9] The written description rejection of claims 1 and 39-44 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Beginning at p. 14 of the instant remarks, applicant argues:

"To expedite prosecution, claim 1 has been amended to remove the term "surrogate" and to feature at least one set of x, y, and z atomic coordinates from Table 5, or a mathematical modification of Table 5 that preserves the relative relationships among the coordinates of Table 5. One skilled in the art would understand that the coordinates from Table 5 could be mathematically modified in such a way as to preserve the relative relationships between the coordinates (e.g., by rotational or translational modification), resulting in the generation of an equivalent three-dimensional structure of a Polo-box domain of a Plk-1 Polo-like kinase...Claim 1 as amended features at least one set of x, y, and z atomic coordinates from Table 5 for each of H-538, K-540, W-414, and L-491...As amended, claim 1 features the coordinates of Table 5, or any mathematical modifications of Table 5 that preserve the relative relationships among the coordinates, from a given atom of each of residues His-538, Lys-540, Trp-414, and Leu-491 of a Polo-box domain of a Plk-1 Polo-like kinase. Accordingly, the rejection of claims 1 and 39-44 under 35 U.S.C. § 112, first paragraph, for lack of written description, may now be withdrawn".

Applicant's argument is not found persuasive. The amendment to the claims is acknowledged. However, even in view of the amendment, claim 1 encompasses a computer having only one set of x, y, and z atomic coordinates from Table 5 for each of

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His-538, Lys-540, Trp-414, and Leu-491 of a Polo-box domain of any Plk-1 Polo-like kinase. (As noted in a previous Office action, His-538, Lys-540, Trp-414, and Leu-491 correspond to His-185, Lys-187, Trp-61, and Leu-138 of Table 5; see, *e.g.*, applicant remarks filed on 5/11/07 at pp. 13-14 and Office action filed on 8/6/07 at p. 3, paragraph 8). The “at least one set of x, y, and z atomic coordinates” can be broadly, but reasonably interpreted as the x, y, and z atomic coordinates of only a single atom of each of His-538, Lys-540, Trp-414, and Leu-491. Thus, claim 1 has been interpreted as encompassing a computer comprising the x, y, and z atomic coordinates for as few as a single atom of each of His-538, Lys-540, Trp-414, and Leu-491 and any other atomic coordinates. While claims 39-42 further limit the “set” to two sets, three sets, four sets or five sets, respectively, it is noted that the atomic coordinates of Table 5 list 10 atoms for His-538, list 9 atoms for Lys-540, list 14 atoms for Trp-414, and list 8 atoms for Leu-491. As such, the claims do not even require the complete atomic coordinates for any of His-538, Lys-540, Trp-414, and Leu-491.

As noted in the prior Office action, the Court of Appeals for the Federal Circuit has held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*,

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structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single species of the genus of claimed computers, *i.e.*, a computer comprising a processor in communication with a memory; said memory having stored therein the structural coordinates of Table 5 and a program for generating a 3-D model of the coordinates. Other than this single disclosed species, the specification fails to disclose any other additional representative species of the claimed genus. As noted above, the genus of atomic coordinates is not even required to have the atomic coordinates of residues His538, Lys540, Trp414, and Leu491, but only a single atom, *i.e.*, an x, y, and z coordinate, for each of His-538, Lys-540, Trp-414, and Leu-491 from Table 5. In this case, the genus of claimed computers encompasses species that are widely variant with respect to the structural coordinates that are stored thereon, representing the three-dimensional structures of polypeptides having any function, including polypeptides that are structurally and functionally unrelated to the Polo-box domain of Plk-1 as disclosed in the instant specification.

Even assuming *arguendo* the resulting variant atomic coordinates and corresponding 3-D structures were limited to a Polo-box domain, it is noted that, while

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methods of generating homology models were known in the art at the time of the invention, possession may not be shown by merely describing how to obtain members of a recited genus or how to identify their common structural features. See *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895. In this case, the specification fails to disclose even a single homologous structure of the Plk1 having the structural coordinates of Table 5 that maintains the conformation of a biologically-active Plk1 polypeptide. According to MPEP § 2163.II.2.(a).ii), “[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.” In this case, the disclosure of the single species as noted above fails to reflect the substantial variation among the species encompassed by the genus of claimed computers.

Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[10] The scope of enablement rejection of claims 1 and 39-44 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Beginning at p. 16 of the instant remarks, applicant argues:

“To expedite prosecution, claim 1 has been amended to feature a computer with a processor in communication with a memory with at least one set of x, y, and z atomic

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coordinates from Table 5, or a mathematical modification of Table 5 that preserves the relative relationships among the coordinates of Table 5, for each of H-538, K-540, W-414, and L-491. Applicants submit that amended claim 1 and claims dependent therefrom are Commensurate in scope with the specification as filed.

Likewise, the working example and guidance provided by the specification as filed are enabling for amended claim 1. Applicants submit that the guidance and working example provided by the specification as filed adequately describe and enable the generation of a three-dimensional model of a Polo-box domain of a Plk-1 Polo-like kinase...

As an initial matter, claim 1, as amended, features a program for generating a three-dimensional model of a Polo-box domain of a Plk-1 Polo-like kinase utilizing the coordinates of Table 5, or mathematical modifications of these coordinates that preserve the relative relationships among the coordinates. Thus, the atomic coordinates and structure generated therefrom of amended claim 1 would enable one of ordinary skill in the art to identify modulators of Plk- 1.

Turning to the teachings of Flower and Lambert,... Flower, however, also teaches (page 25) that, when a protein structure has been generated through homology modeling, "one can dock small or large molecules.., or one can perform some kind of atomistic simulation leading, in turn, to the investigation of thermodynamic properties, principally binding." Thus, Flower teaches that homology modeling is "a well-established technique" that can be useful in the identification of molecules that bind to a given protein... Applicants direct the Examiner's attention to Lambert (page 17), which states: "[T]he structure coordinates of a crystalline PPAR α [ligand-binding domain] LBD can be used to design compounds that bind to a PPAR LBD (more preferably a PPAR α LBD) and alter the properties of a PPAR LBD..." The teachings of Lambert suggest that the PPAR α structure may serve as a model for any other PPAR subtype for the purpose of identifying compounds that alter PPAR activity. As such, Applicants submit that the teachings of Flower and Lambert do not dismiss homology modeling as a means of identifying modulators of a given protein.

With respect to the quantity of experimentation required,... Applicants submit that claim 1, as amended, would not have required undue experimentation at the time of filing. With the specification in hand, practicing claim 1, as amended, would have been routine to one of ordinary skill in the art. Thus, in view of the present amendment to claim 1 and claims dependent therefrom, the rejection under 35 U.S.C. § 112, first paragraph, for insufficient scope of enablement may now be withdrawn.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification, while being enabling for a computer comprising a processor in communication with a memory; said memory having stored therein the structural coordinates of Table 5 and a program for generating a 3-D model of the polypeptide represented by the coordinates, does not reasonably provide enablement for all computers as encompassed by the claims.

As noted above, the amendment to the claims is acknowledged. However, even in view of the amendment, claim 1 encompasses a computer having only one set of x, y, and z atomic coordinates from Table 5 for each of His-538, Lys-540, Trp-414, and Leu-491 of a Polo-box domain of any Plk-1 Polo-like kinase. (As noted in a previous Office action, His-538, Lys-540, Trp-414, and Leu-491 correspond to His-185, Lys-187, Trp-61, and Leu-138 of Table 5; see, e.g., applicant remarks filed on 5/11/07 at pp. 13-14 and Office action filed on 8/6/07 at p. 3, paragraph 8). The “at least one set of x, y, and z atomic coordinates” can be broadly, but reasonably interpreted as the x, y, and z atomic coordinates of only a single atom of each of His-538, Lys-540, Trp-414, and Leu-491. Thus, claim 1 has been interpreted as encompassing a computer comprising the x, y, and z atomic coordinates for as few as a single atom of each of His-538, Lys-540, Trp-414, and Leu-491 and any other atomic coordinates. While claims 39-42 further limit the “set” to two sets, three sets, four sets or five sets, respectively, it is noted that the atomic coordinates of Table 5 list 10 atoms for His-538, list 9 atoms for Lys-540, list 14 atoms for Trp-414, and list 8 atoms for Leu-491. As such, the claims do not even require the complete atomic coordinates for any of His-538, Lys-540, Trp-414, and Leu-491.

As noted in previous Office actions and undisputed by applicant, the specification provides only a single working example of atomic coordinates of a “Polo-box domain of a Plk-1 Polo-like kinase”, *i.e.*, the atomic coordinates of Table 5. Moreover, the specification fails to provide any specific guidance for using the x, y, and z atomic coordinates of only a single atom of each of His-538, Lys-540, Trp-414, and Leu-491 in combination with any other structural coordinates with an expectation that these atomic

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coordinates will achieve a 3-D representation of a “Polo-box domain of a Plk-1 Polo-like kinase”. Although applicant argues that homology modeling techniques were useful at the time of the invention, this is not at issue. The issue is whether or not all atomic coordinates as encompassed by the claims can be used with an expectation of achieving a 3-D representation of a “Polo-box domain of a Plk-1 Polo-like kinase” for use in identifying inhibitors thereof (specification at p. 1, lines 20-22). At the time of the invention, the use of homology models for identifying such inhibitors was employed, however, whether the homology model maintained the desired 3-D conformation was highly unpredictable as evidenced by the references of Flower and Lambert (cited in the PTO-892 filed on 12/6/06). As noted in prior Office actions, it was *not* routine at the time of the invention to generate the atomic coordinates as broadly encompassed by the claims, particularly as the specification fails to provide guidance for making and using all homology models as encompassed by the claims with no expectation that the resulting models maintain a biologically-relevant 3-D conformation of a Plk1 polypeptide.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24

(CCPA 1970)). Without sufficient guidance, determination of having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

[11] The rejection of claims 1 and 39-44 under 35 U.S.C. 102(b) as being anticipated by Armistead et al. (US Patent 5,978,740) is withdrawn in view of the instant claim amendment.

Claim Rejections - 35 USC § 103

[12] The rejection of claims 1 and 39-44 under 35 U.S.C. 103(a) as being unpatentable over Armistead et al. (US Patent 5,978,740) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Beginning at p. 19 of the instant remarks, applicant argues:

As an initial matter, Applicants submit that the Examiner mischaracterizes the teachings of *Gulack*. In *Gulack*, the device claim at issue features three components: a band or ring, a plurality of digits imprinted on the band ("printed matter"), and an algorithm for generating the digits. The Court acknowledges that a functional relationship exists between the band and printed matter, stating:

Under section 103, the board cannot dissect a claim, excise the printed matter from it, and declare the remaining portion of the mutilated claim to

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be unpatentable. The claim must be read as a whole. (*Id.*, 703 F.2d at 1365)

In addition, the Federal Circuit recites additional criteria for patentability, stating that "the critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate" (*Id.*, 703 F.2d at 1386).

Applying the teachings of *Gulack* to the present invention, it is improper to excise the atomic coordinates from claim 1, determine them to be "nonfunctional descriptive material," and declare the claim as a whole to be unpatentable. The generation of the three-dimensional protein structure of the present invention is a function of the computer acting upon the claimed atomic coordinates stored in its memory and outputting the coordinates in the form of a novel and useful model. Thus, a new and nonobvious functional relationship exists between the computer and coordinates.

Turning to *Ngai*, the Federal Circuit held that "a set of instructions into a known kit does not interrelate with the kit in the same way as the numbers interrelated with the band" (*Id.*, 367 F.3d at 1336). The Court further notes:

In *Gulack*, the printed matter would not achieve its educational purposes without the band, and the band without the printed matter would similarly be unable to produce the desired result. Here, the printed matter in no way depends on the kit, and the kit does not depend on the printed matter. (*Id.*, 367 F.3d at 1336)

Using the same logic as presented by the Court in the *Ngai* opinion, the atomic coordinates of the present invention would not achieve their purpose (e.g., educational or industrial) without the computer outputting a representation of the structural model, and the computer without the atomic coordinates would similarly be unable to produce the desired result. Thus, in view of the present amendment to claim 1 and claims dependent therefrom, the rejection under 35 U.S.C. § 103(a) may now be withdrawn.

Applicant's argument is not found persuasive. The examiner maintains the position that the recited atomic coordinates are non-functional descriptive material. Applicant asserts the examiner has improperly applied *Gulack*. However, contrary to applicant's assertion, the examiner has correctly applied *Gulack* in the obviousness analysis of the claimed invention. As noted in *Gulack* and acknowledged by applicant, "the critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate". While applicant argues "The generation of the three-dimensional protein structure of the present invention is a

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function of the computer”, the presence of the Table 5 data stored in the computer’s memory would not appear to alter the function of the computer. Although applicant argues the atomic coordinate data of Table 5 “would not achieve their purpose...without the computer...and the computer without the atomic coordinates would similarly be unable to produce the desired result”, the computer would appear to function in the same way regardless of whether or not the data of Table 5 were stored on the computer’s memory. In other words, the computer would appear to function independently of the atomic coordinate data of Table 5.

For reasons of record, the data of Table 5 are considered to be non-functional descriptive material and in view of the teachings of the cited prior art and in view of the Court’s holding in *In re Gulack* and *In re Ngai*, the claimed computer would have been obvious to one of ordinary skill in the art at the time of the invention. See also Case 2 of Annex 3: Comments of the USPTO at pp. 63-64 of the Trilateral Project WM4 Comparative studies in new technologies, Theme: Comparative study on “protein 3-dimensional (3-D) structure related claims” (cited in the PTO-892 filed on 12/6/06).

Conclusion

[13] Status of the claims:

Claims 1-13, 17-25, 27-36, and 39-44 are pending.

Claims 2-13, 17-25, and 27-36 are withdrawn from consideration.

Claims 1 and 39-44 are rejected.

No claim is in condition for allowance.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
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